Carta Trámite

20 de julio de 2021

A: Todos los Proveedores Contratados por First Medical Health Plan, Inc. para el Plan Vital, Región Única y Población Vital-X (Virtual)

Re: Carta Normativa 21-0719-01 relacionada a Desautorización del Uso de Bamlanivimab y Estesevimab ante pausa en el EUA emitida por ASPR y FDA

Estimado(a) Proveedor(a):

Reciba un cordial saludo de parte de First Medical Health Plan, Inc. (FMHP).

Adjunto a este comunicado encontrará la Carta Normativa 21-0719-01 de la Administración de Seguros de Salud de Puerto Rico (ASES).

A través de esta Carta Normativa, la ASES informa que, deja sin efecto la Carta Normativa 20-1218, emitida el 18 de diciembre de 2020, referente a la Guía Clínica para la Administración de Bamlanivimab y REGN-COV2. Esto según el comunicado emitido por el Departamento de Salud y Servicios Humanos de Estados Unidos (HHS, por sus siglas en inglés), *Assistance Secretary for Preparedness and Response (ASPR) and the Food and Drug Administration (FDA).* La ASES aclara que la EUA para el REGEN-COV permanece inalterada y su uso sigue autorizado bajo el EUA 091.

Códigos HCPCS

La droga etesevimab no tiene código HCPCS ya que no ha sido autorizada como monoterapia. La combinación de etesevimab + banlanivimab tiene los siguientes códigos:

Code	CPT Short Descriptor	Labeler Name	Vaccine/ Procedure Name
Q0245	Bamlanivimab and etesevimab	Eli Lilly	Injection, banlanivimab, 2100 mg
M0245	Bamlan and etesev infusion	Eli Lilly	Intravenous infusion, bamlanivimab and etesevimab, includes infusion and post administration monitoring
M0246	Bamlan and etesev infus home	Eli Lilly	Intravenous infusion, sotrovimab, bamlanivimab and etesevimab, includes infusion and post administration monitoring in the home that has been made provider-based to the hospital during the covid-19 public health emergency

Para obtener información adicional, se recomienda acceder al siguiente enlace: https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/covid-19-vaccines-and-monocional-antibodies.

La ASES indica que, no estará autorizando pago por la administración de Banlanivimab y Etesivimab a partir de la fecha de esta comunicación ya que se ha pausado su distribución según las recomendaciones y el comunicado del "Assitance Secretary for Preparedness and Response (ASPR) and the Food and Drug Administration (FDA)".

Para referencia se incluyen los siguientes documentos: *Emergency Use Authorization (EUA) of Bamlanivimab and Etesevimab* y la Carta Normativa 20-1218 Guía Clínica Administración Bamlanivimab y REGN-COV2.

Para detalles específicos sobre la información provista por la ASES, le exhortamos a leer detenidamente la Carta Normativa 21-0719-01.

Si usted tiene alguna pregunta relacionada a este comunicado y/o necesita información adicional, siéntase en la libertad de comunicarse con nuestro Centro de Servicio al Proveedor al número libre de cargos 1-844-347-7802 de lunes a viernes de 7:00 a.m. a 7:00 p.m. También, puede acceder a www.firstmedicalvital.com.

Cordialmente,

Departamento de Cumplimiento
First Medical Health Plan, Inc.

GOBIERNO DE PUERTO RICO
ADMINISTRACIÓN DE SEGUROS DE SALUD
Director Ejecutivo I Jorge E. Galva, JD, MHA I jgalva@asespr.org

CARTA NORMATIVA 21-0719-01

19 de julio de 2021

A: **ORGANIZACIONES DE MANEJO DE CUIDADO DIRIGIDO, GRUPOS MÉDICOS, MÉDICOS PRIMARIOS, FARMACIAS Y PROVEEDORES PARTICIPANTES DEL PLAN DE SALUD DEL GOBIERNO - PLAN VITAL**

RE: **DESAUTORIZACIÓN DEL USO DE BAMLANIVIMAB Y ETESEVIMAB ANTE PAUSA EN EL EUA EMITIDA POR ASPR Y FDA**

Anteriormente, a Administración de Drogas y Alimentos (FDA por sus siglas en inglés), autorizó el uso de **bamlanivimab** y **etesevimab** bajo el mecanismo de uso de emergencias (EUA), para ser administrados **combinados** en pacientes con COVID 19 leve a moderada, y a partir de los 12 años y con un peso de 40 kg (88 lbs.) o más. Con resultado positivo a prueba viral directa SARS-CoV-2 y que se encuentren dentro del grupo denominado de alto riesgo para progresar a un estadio severo de COVID-19 y /o requerir hospitalización.

Sin embargo, el 25 de junio de 2021, el Departamento de Salud y Servicios Humanos de Estados Unidos (HHS por sus siglas en inglés) emitió el siguiente comunicado ante las recomendaciones de **Assistant Secretary for Preparedness and Response (ASPR) and the Food and Drug Administration (FDA)**[1] el cual, citamos en inglés según circulado:

> *"Today, we are informing you that ASPR is immediately pausing all distribution of bamlanivimab and etesevimab together and etesevimab alone (to pair with existing supply of bamlanivimab at a facility for use under EUA 094) on a national basis until further notice. In addition, FDA recommends that health care providers nationwide use alternative authorized monoclonal antibody therapies, as described below, and not use bamlanivimab and etesevimab administered together at this time."*
> *"The Centers for Disease Control and Prevention (CDC) has identified that the combined frequencies of the SARS-CoV-2 P.1/Gamma variant (first identified in Brazil) and the B.1.351/Beta variant (first identified in South Africa) throughout the United States now exceed 11% and are trending upward (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html). Results from in vitro assays that are used to assess the susceptibility of viral variants to monoclonal antibodies suggest that bamlanivimab and etesevimab administered together are not active against either the P.1 or B.1.351 variants.*

[1] https://www.phe.gov/emergency/events/COVID19/therapeutics/Pages/default.aspx

These assays use "pseudotyped virus-like particles" that help determine likely susceptibility of the live SARS-CoV-2 variant viruses."
"REGEN-COV and sotrovimab are alternative monoclonal antibody therapies that are currently authorized for the same use as bamlanivimab and etesevimab administered together. Based on similar in vitro assay data currently available, REGEN-COV and sotrovimab are likely to retain activity against the P.1 or B.1.351 variants. All treatment delivery sites can continue ordering REGEN-COV from the authorized distributer by following the existing ordering and reporting procedures. All treatment sites may also find information on the availability and ordering of sotrovimab by visiting GlaxoSmithKline's website at www.sotrovimab.com."

Ante esta nueva directriz, la Administración de Seguros de Salud (ASES) **deja sin efecto la Carta Normativa 20-1218, emitida el 18 de diciembre de 2020, referente a la GUÍA CLÍNICA PARA LA ADMINISTRACIÓN DE BAMLANIVIMAB Y REGN-COV2.** Aclaramos que la EUA para el REGEN-COV permanece inalterada y su uso sigue autorizado bajo el EUA 091, según revisado 6/3/2021.

Códigos HCPS

La droga etesivimab no tiene código HCPCS ya que no ha sido autorizada como monoterapia. La combinación de **etesivimab + bamlanivimab** tiene los siguientes códigos

Code	CPT Short Descriptor	Labeler Name	Vaccine/Procedure Name
Q0245	Bamlanivimab and etesevima	Eli Lilly	Injection, bamlanivimab and etesevimab, 2100 mg
M0245	Bamlan and etesev infusion	Eli Lilly	intravenous infusion, bamlanivimab and etesevimab, includes infusion and post administration monitoring
M0246	Bamlan and etesev infus home	Eli Lilly	Intravenous infusion, bamlanivimab and etesevimab, includes infusion and post administration monitoring in the home or residence; this includes a beneficiary's home that has been made provider-based to the hospital during the covid-19 public health emergency

Pueden obtener a información actualizada sobre este particular accediendo: https://www.cms.gov/medicare/medicare-part-b-drug-average-sales-price/covid-19-vaccines-and-monoclonal-antibodies.

Es importante que tenga presente que la ASES no estará autorizando pago por la administración de **bamlanivimab** y **etesevimab** a partir de la fecha de esta comunicación ya que se ha pausado su distribución según las recomendaciones y el comunicado del "**Assistant Secretary for Preparedness and Response (ASPR) and the Food and Drug Administration (FDA)".**

Se incluye para referencia, copia de la CN-20-1218 y la hoja informativa titulada *Fact Sheet for Healthcare Providers Emergency Use Authorization (EUA) of BAMLANIVIMAB and ETESEVIMAB*. La ASES les requiere a todas las aseguradoras bajo el Plan de Salud del Gobierno – Plan Vital comunicar y distribuir a la brevedad posible esta información entre sus proveedores contratados.

Cordialmente,

Madeline Figueroa Rivera, JD, MA
Directora Ejecutiva Interina

Anejos (2)

FACT SHEET FOR HEALTH CARE PROVIDERS
EMERGENCY USE AUTHORIZATION (EUA) OF BAMLANIVIMAB AND ETESEVIMAB

AUTHORIZED USE

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved products bamlanivimab and etesevimab administered together for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

RECENT MAJOR CHANGES

• Definition of High Risk for Disease Progression (Box and Section 2.1) – definition has been expanded to include additional medical conditions and other factors.	Revised 05/2021
• Dosage and Administration, Dosage (Section 2.2) – removal of rationale for authorized dose because Phase 3 data have confirmed the authorized dose.	Revised 05/2021
• Overall Safety Summary, Clinical Trials Experience (Section 6.1) – updated to integrated clinical trial safety analyses focused on adverse reactions and most common treatment-emergent adverse events.	Revised 05/2021
• Antiviral Resistance (Box and Section 15) – addition of information on susceptibility of SARS-CoV-2 variants to bamlanivimab and etesevimab (Table 3 and Table 4).	Revised 03/2021 and 05/2021
• Clinical Trial Results and Supporting Data for EUA, Mild to Moderate COVID-19 (BLAZE-1) (Section 18.1) – addition of Phase 3 data for the authorized dose.	Revised 05/2021

LIMITATIONS OF AUTHORIZED USE

- Bamlanivimab and etesevimab are not authorized for use in patients:
  - who are hospitalized due to COVID-19, OR
  - who require oxygen therapy due to COVID-19, OR
  - who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.
- Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab and etesevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Bamlanivimab and etesevimab have been authorized by FDA for the emergency uses described above.

Bamlanivimab and etesevimab are not FDA-approved for these uses.

Bamlanivimab and etesevimab are authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of bamlanivimab and etesevimab under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

This EUA is for the use of the unapproved products bamlanivimab and etesevimab administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization *[see Limitations of Authorized Use]*.

The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example age ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of bamlanivimab and etesevimab under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies. Health care providers should review the Antiviral Resistance

information in Section 15 of this Fact Sheet for details regarding specific variants and resistance, and refer to the CDC website (https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html) as well as information from state and local health authorities regarding reports of viral variants of importance in their region to guide treatment decisions.

Under this EUA, bamlanivimab and etesevimab must be administered together after dilution by intravenous (IV) infusion only.

Bamlanivimab and etesevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

Health care providers must submit a report on all medication errors and **ALL SERIOUS ADVERSE EVENTS** potentially related to bamlanivimab and etesevimab. See Sections 8 and 9 of the Full EUA Prescribing Information for reporting instructions below.

- The authorized dosage is 700 mg bamlanivimab and 1,400 mg of etesevimab administered together as a single intravenous (IV) infusion as soon as possible after positive viral test for SARS-CoV-2 and within ten days of symptom onset *[see Dosage and Administration (2.2) and Clinical Trial Results and Supporting Data for EUA (18.1)]*.
- Bamlanivimab and etesevimab are both available as solutions in separate vials and must be diluted and combined prior to administration.
- To prepare the dose you will need 1 vial of bamlanivimab and 2 vials of etesevimab.
- Administer bamlanivimab and etesevimab together as a single intravenous (IV) infusion via pump or gravity (see **Table 1** and **Table 2**).
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.
- Patients treated with bamlanivimab and etesevimab together should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines.

The authorized dosage may be updated as additional data from clinical trials becomes available.

For information on clinical trials that are testing the use of bamlanivimab and etesevimab in COVID-19, please see www.clinicaltrials.gov.

Contraindications
None.

Dosing

BAMLANIVIMAB AND ETESEVIMAB MUST BE ADMINISTERED TOGETHER AFTER DILUTION BY INTRAVENOUS (IV) INFUSION ONLY.

Patient Selection and Treatment Initiation

This section provides essential information on the unapproved products bamlanivimab and etesevimab administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization *[see Limitations of Authorized Use]*.

The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example age ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of bamlanivimab and etesevimab under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

Dosage

The dosage of bamlanivimab and etesevimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) is *[see Clinical Trial Results and Supporting Data for EUA (18.1)]*:

- bamlanivimab 700 mg

- etesevimab 1,400 mg.

Administer bamlanivimab and etesevimab together as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset.

Under this EUA, bamlanivimab and etesevimab must be diluted and administered together as a single intravenous infusion.

Dosage Adjustment in Specific Populations
No dosage adjustment is recommended based on age, sex, race, body weight, renal or mild hepatic impairment, during pregnancy or while lactating, or for disease severity or inflammation *[see Full EUA Prescribing Information, Use in Specific Populations (11)]*.

Preparation and Administration
Preparation
Bamlanivimab and etesevimab solution for infusion should be prepared by a qualified healthcare professional using aseptic technique:

- Gather the materials for preparation:
  - Polyvinyl chloride (PVC) or polyethylene (PE)-lined PVC, sterile prefilled infusion bag. Choose one of the following sizes:
    - Prefilled 50 mL, 100 mL, 150 mL, or 250 mL infusion bag containing 0.9% Sodium Chloride Injection (see **Table 1** and **Table 2**).
  - One vial of bamlanivimab (700 mg/20 mL) and two vials of etesevimab (700 mg/20 mL).
- Bamlanivimab and etesevimab are supplied in individual single-dose vials but are administered together using a single infusion bag.
- Remove 1 bamlanivimab vial and 2 etesevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vials.**
- Inspect both bamlanivimab and etesevimab vials visually for particulate matter and discoloration.
  - Bamlanivimab and etesevimab are clear to opalescent and colorless to slightly yellow to slightly brown solutions.
- Withdraw 20 mL from one bamlanivimab vial and 40 mL from two etesevimab vials and inject all 60 mL into a prefilled infusion bag containing 0.9% Sodium Chloride (see **Table 1** or **Table 2**).
- Discard any product remaining in the vials.
- Gently invert the bag by hand approximately 10 times to mix. **Do not shake.**
- These products are preservative-free and therefore, the diluted infusion solution should be administered immediately.
  - If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) and up to 7 hours at room temperature (20°C to 25°C [68°F to 77°F]) including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.

Administration

Bamlanivimab and etesevimab infusion solution should be administered by a qualified healthcare professional.

- Gather the materials for infusion:
  - Polyvinyl chloride (PVC) or polyethylene (PE)-lined PVC infusion set.
  - Use of an in-line or add-on 0.2/0.22 micron polyethersulfone (PES) filter is strongly recommended.
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity according to the size of infusion bag used (see **Table 1 for patients weighing ≥50 kg** or **Table 2 for patients weighing <50 kg**). Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of bamlanivimab and etesevimab injection with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride to ensure delivery of the required dose.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.
- If the infusion must be discontinued due to an infusion reaction, discard any unused product.
- The use of closed system transfer devices (CSTDs), elastomeric pumps, and pneumatic transport with bamlanivimab has not been studied.

Table 1: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion[a] in Patients Weighing 50 kg or More

Drug[a]: Add 20 mL of bamlanivimab (1 vial) and 40 mL of etesevimab (2 vials) for a total of 60 mL to a prefilled infusion bag and administer as instructed below		
Size of Prefilled 0.9% Sodium Chloride Infusion Bag	**Maximum Infusion Rate**	**Minimum Infusion Time**
50 mL	310 mL/hr	21 minutes
100 mL	310 mL/hr	31 minutes
150 mL	310 mL/hr	41 minutes
250 mL	310 mL/hr	60 minutes

[a] 700 mg of bamlanivimab and 1,400 mg of etesevimab are added to the same infusion bag and administered together as a single intravenous infusion.

Table 2: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion in Patients Weighing Less Than 50 kg

Drug[a]: Add 20 mL of bamlanivimab (1 vial) and 40 mL of etesevimab (2 vials) for a total 60 mL to an infusion bag and administer as instructed below		
Size of Prefilled 0.9% Sodium Chloride Infusion Bag	**Maximum Infusion Rate**	**Minimum Infusion Time**
50 mL	310 mL/hr	21 minutes
100 mL	310 mL/hr	31 minutes
150 mL	310 mL/hr	41 minutes
250 mL[b]	266 mL/hr	70 minutes

[a] 700 mg of bamlanivimab and 1,400 mg of etesevimab are added to the same infusion bag and administered together as a single intravenous infusion.

[b] The minimum infusion time for patients weighing less than 50 kg who are administered bamlanivimab and etesevimab together using the 250 mL prefilled 0.9% Sodium Chloride infusion bag must be extended to at least 70 minutes to ensure safe use (endotoxin load).

Storage

Refrigerate unopened vials at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze, shake, or expose to direct light.

Warnings

There are limited clinical data available for bamlanivimab and etesevimab. Serious and unexpected adverse events may occur that have not been previously reported with use of bamlanivimab and etesevimab together.

Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of bamlanivimab with and without etesevimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy.

Infusion-related reactions have been observed with administration of bamlanivimab and etesevimab together. These reactions may be severe or life threatening.

Signs and symptoms of infusion related reactions may include:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness and diaphoresis.

If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.

Clinical Worsening After Bamlanivimab Administration

Clinical worsening of COVID-19 after administration of bamlanivimab has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered

mental status. Some of these events required hospitalization. It is not known if these events were related to bamlanivimab use or were due to progression of COVID-19.

Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19
Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab and etesevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation. Therefore, bamlanivimab and etesevimab are not authorized for use in patients *[see Limitations of Authorized Use]*:

- who are hospitalized due to COVID-19, OR
- who require oxygen therapy due to COVID-19, OR
- who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

Side Effects
Adverse events have been reported with bamlanivimab and etesevimab *[see Full EUA Prescribing Information, Overall Safety Summary (6.1)]*.

Additional adverse events associated with bamlanivimab and etesevimab, some of which may be serious, may become apparent with more widespread use.

INSTRUCTIONS FOR HEALTHCARE PROVIDERS
As the healthcare provider, you must communicate to your patient or parent/caregiver, as age appropriate, information consistent with the "Fact Sheet for Patients, Parents and Caregivers" (and provide a copy of the Fact Sheet) prior to the patient receiving bamlanivimab and etesevimab, including:

- FDA has authorized the emergency use of bamlanivimab and etesevimab administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization *[see Limitations of Authorized Use]*.
- The patient or parent/caregiver has the option to accept or refuse bamlanivimab and etesevimab.
- The significant known and potential risks and benefits of bamlanivimab and etesevimab, and the extent to which such potential risks and benefits are unknown.
- Information on available alternative treatments and the risks and benefits of those alternatives, including clinical trials.
- Patients treated with bamlanivimab and etesevimab together should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines.

For information on clinical trials that are testing the use of bamlanivimab and etesevimab together for COVID-19, please see www.clinicaltrials.gov.

MANDATORY REQUIREMENTS FOR BAMLANIVIMAB AND ETESEVIMAB ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION:
In order to mitigate the risks of using these unapproved products and to optimize the potential benefit of bamlanivimab and etesevimab under this EUA, the following items are required. Use of bamlanivimab and etesevimab under this EUA is limited to the following (all requirements **must** be met):

1. Treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization *[see Limitations of Authorized Use]*.
2. As the healthcare provider, communicate to your patient or parent/caregiver, as age appropriate, information consistent with the "Fact Sheet for Patients, Parents and Caregivers" prior to the patient receiving bamlanivimab and etesevimab. Healthcare providers (to the extent practicable given the circumstances of the emergency) must document in the patient's medical record that the patient/caregiver has been:
   a. Given the "Fact Sheet for Patients, Parents and Caregivers",
   b. Informed of alternatives to receiving authorized bamlanivimab and etesevimab, and
   c. Informed that bamlanivimab and etesevimab are unapproved drugs that are authorized for use under this Emergency Use Authorization.
3. Patients with known hypersensitivity to any ingredient of bamlanivimab or etesevimab must not receive bamlanivimab and etesevimab.
4. The prescribing health care provider and/or the provider's designee is/are responsible for mandatory reporting of all medication errors and serious adverse events* potentially related to bamlanivimab and etesevimab treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "bamlanivimab and etesevimab use for COVID-19 under Emergency Use Authorization (EUA)" in the description section of the report.

   - Submit adverse event reports to FDA MedWatch using one of the following methods:
     - Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
     - Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
       - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
       - Fax (1-800-FDA-0178), or
     - Call 1-800-FDA-1088 to request a reporting form.
     - Submitted reports should include in the field name, "Describe Event, Problem, or Product Use/Medication Error" the statement "bamlanivimab and etesevimab use for COVID-19 under Emergency Use Authorization (EUA)"

   *Serious Adverse Events are defined as:
   - death;
   - a life-threatening adverse event;

- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

5. The prescribing health care provider and/or the provider's designee is/are to provide mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of bamlanivimab and etesevimab.
6. OTHER REPORTING REQUIREMENTS
    - Healthcare facilities and providers must report therapeutics information and utilization data through HHS Protect, Teletracking or National Healthcare Safety Network (NHSN) as directed by the U.S. Department of Health and Human Services.

    - In addition, please provide a copy of all FDA MedWatch forms to:
      Eli Lilly and Company, Global Patient Safety
      Fax: 1-317-277-0853
      E-mail: mailindata_gsmtindy@lilly.com
      Or call Eli Lilly and Company at 1-855-LillyC19 (1-855-545-5921) to report adverse events.

APPROVED AVAILABLE ALTERNATIVES

There is no adequate, approved and available alternative to bamlanivimab and etesevimab administered together for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. Additional information on COVID-19 treatments can be found at https://www.cdc.gov/coronavirus/2019-ncov/index.html. The health care provider should visit https://clinicaltrials.gov/ to determine whether the patient may be eligible for enrollment in a clinical trial.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of the Department of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 pandemic. FDA has issued this EUA, requested by Eli Lilly and Company for the unapproved products bamlanivimab and etesevimab administered together for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe

COVID-19 and/or hospitalization.[1] As a health care provider, you must comply with the mandatory requirements of the EUA (see above).

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that bamlanivimab and etesevimab administered together may be effective for the treatment of mild to moderate COVID-19 in certain high-risk patients as specified in this Fact Sheet. You may be contacted and asked to provide information to help with the assessment of the use of the product during this emergency.

This EUA for bamlanivimab and etesevimab will end when the Secretary determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed.

CONTACT INFORMATION
For additional information visit
www.BAMandETE.com

If you have questions, please contact
1-855-LillyC19 (1-855-545-5921)

END SHORT VERSION FACT SHEET
Long Version Begins on Next Page

[1] The health care provider should visit clinicaltrials.gov to determine whether there is an active clinical trial for the product in this disease/condition and whether enrollment of the patient(s) in a clinical trial is more appropriate than product use under this EUA.

FULL EUA PRESCRIBING INFORMATION

FULL EUA PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

1 AUTHORIZED USE

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved products bamlanivimab and etesevimab administered together for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization.

LIMITATIONS OF AUTHORIZED USE

- Bamlanivimab and etesevimab are not authorized for use in patients:
  - who are hospitalized due to COVID-19, OR
  - who require oxygen therapy due to COVID-19, OR
  - who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.
- Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such as bamlanivimab and etesevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation *[see Warnings and Precautions (5.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Bamlanivimab and etesevimab should be administered together as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progressing to severe COVID-19 and/or hospitalization.

The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example age ≥65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m^2, or if age 12-17, have BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19))

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and authorization of bamlanivimab and etesevimab under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html. Healthcare providers should consider the benefit-risk for an individual patient.

2.2 Dosage

The dosage of bamlanivimab and etesevimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) is *[see Clinical Trial Results and Supporting Data for EUA (18.1)]*:

- bamlanivimab 700 mg
- etesevimab 1,400 mg.

Administer bamlanivimab and etesevimab together as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset.

Under this EUA, bamlanivimab and etesevimab must be diluted and administered together as a single intravenous infusion.

2.3 Dosage Adjustment in Specific Populations

Pregnancy or Lactation
No dosage adjustment is recommended in pregnant or lactating women *[see Use in Specific Populations (11.1, 11.2)]*.

Pediatric Use
No dosage adjustment is recommended in pediatric patients who weigh at least 40 kg and are 12 years of age and older. Bamlanivimab and etesevimab are not authorized for patients weighing less than 40 kg or those less than 12 years of age *[see Use in Specific Populations (11.3)]*.

Geriatric Use
No dosage adjustment is recommended in geriatric patients *[see Use in Specific Populations (11.4)]*.

Renal Impairment
No dosage adjustment is recommended in patients with renal impairment *[see Use in Specific Populations (11.5)]*.

Hepatic Impairment
No dosage adjustment is recommended in patients with mild hepatic impairment. Bamlanivimab and etesevimab has not been studied in patients with moderate or severe hepatic impairment *[see Use in Specific Populations (11.6)]*.

2.4 Dose Preparation and Administration

Preparation
Bamlanivimab and etesevimab solution for infusion should be prepared by a qualified healthcare professional using aseptic technique:

- Gather the materials for preparation:
  - Polyvinyl chloride (PVC) or polyethylene (PE)-line PVC, sterile infusion bag. Choose one of the following sizes:
    - Prefilled 50 mL, 100 mL, 150 mL, or 250 mL infusion bag containing 0.9% Sodium Chloride Injection (see **Table 1** and **Table 2**).
  - One vial of bamlanivimab (700 mg/20 mL) and two vials of etesevimab (700 mg/20 mL).
- Bamlanivimab and etesevimab are supplied in individual single-dose vials but are administered together using a single infusion bag.
- Remove 1 bamlanivimab vial and 2 etesevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. **Do not expose to direct heat. Do not shake the vials.**
- Inspect both bamlanivimab and etesevimab vials visually for particulate matter and discoloration.
  - Bamlanivimab and etesevimab are clear to opalescent and colorless to slightly yellow to slightly brown solutions.

- Withdraw 20 mL from one bamlanivimab vial and 40 mL from two etesevimab vials and inject all 60 mL into a prefilled infusion bag containing 0.9% Sodium Chloride (see **Table 1** or **Table 2**).
- Discard any product remaining in the vials.
- Gently invert the bag by hand approximately 10 times to mix. **Do not shake.**
- These products are preservative-free and therefore, the diluted infusion solution should be administered immediately.
    - If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) and up to 7 hours at room temperature (20°C to 25°C [68°F to 77°F]) including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.

Administration

Bamlanivimab and etesevimab infusion solution should be administered by a qualified healthcare professional.

- Gather the materials for infusion:
    - Polyvinyl chloride (PVC) or polyethylene (PE)-lined PVC infusion set
    - Use of an in-line or add-on 0.2/0.22 micron polyethersulfone (PES) filter is strongly recommended.
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer the entire infusion solution in the bag via pump or gravity according to the size of infusion bag used (see **Table 1 for patients weighing ≥50 kg** or **Table 2 for patients weighing <50 kg**). Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of bamlanivimab and etesevimab injection with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride to ensure delivery of the required dose.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.
- If the infusion must be discontinued due to an infusion reaction, discard any unused product.
- The use of closed system transfer devices (CSTDs), elastomeric pumps, and pneumatic transport with bamlanivimab has not been studied.

Table 1: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion[a] in Patients Weighing 50 kg or More

Drug[a]: Add 20 mL of bamlanivimab (1 vial) and 40 mL of etesevimab (2 vials) for a total of 60 mL to a prefilled infusion bag and administer as instructed below		
Size of Prefilled 0.9% Sodium Chloride Infusion Bag	**Maximum Infusion Rate**	**Minimum Infusion Time**
50 mL	310 mL/hr	21 minutes
100 mL	310 mL/hr	31 minutes
150 mL	310 mL/hr	41 minutes
250 mL	310 mL/hr	60 minutes

[a] 700 mg of bamlanivimab and 1,400 mg of etesevimab are added to the same infusion bag and administered together as a single intravenous infusion.

Table 2: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab for IV Infusion[a] in Patients Weighing Less Than 50 kg

Drug[a]: Add 20 mL of bamlanivimab (1 vial) and 40 mL of etesevimab (2 vials) for a total of 60 mL to a prefilled infusion bag and administer as instructed below		
Size of Prefilled 0.9% Sodium Chloride Infusion Bag	**Maximum Infusion Rate**	**Minimum Infusion Time**
50 mL	310 mL/hr	21 minutes
100 mL	310 mL/hr	31 minutes
150 mL	310 mL/hr	41 minutes
250 mL[b]	266 mL/hr	70 minutes

[a] 700 mg of bamlanivimab and 1,400 mg of etesevimab are added to the same infusion bag and administered together as a single intravenous infusion.

[b] The minimum infusion time for patients weighing less than 50 kg who are administered bamlanivimab and etesevimab together using the 250 mL prefilled 0.9% Sodium Chloride infusion bag must be extended to at least 70 minutes to ensure safe use (endotoxin load).

Storage

This product is preservative-free and therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) and up to 7 hours at room temperature (20°C to 25°C [68°F to 77°F]) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.

3 DOSAGE FORMS AND STRENGTHS

Bamlanivimab is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution available as:

- Injection: 700 mg/20 mL (35 mg/mL) as in a single-dose vial.

Etesevimab is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution available as:

- Injection: 700 mg/20 mL (35 mg/mL) in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

There are limited clinical data available for bamlanivimab and etesevimab. Serious and unexpected adverse events may occur that have not been previously reported with use of bamlanivimab and etesevimab together.

5.1 Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of bamlanivimab with and without etesevimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions have been observed with administration of bamlanivimab and etesevimab together. These reactions may be severe or life threatening.

Signs and symptoms of infusion related reactions may include *[see Overall Safety Summary (6.1)]*:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness and diaphoresis.

If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.

5.2 Clinical Worsening After Bamlanivimab Administration

Clinical worsening of COVID-19 after administration of bamlanivimab has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to bamlanivimab use or were due to progression of COVID-19.

5.3 Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19

Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to COVID-19. Monoclonal antibodies, such bamlanivimab and etesevimab, may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical

ventilation. Therefore, bamlanivimab and etesevimab are not authorized for use in patients *[see Limitations of Authorized Use]*:

- who are hospitalized due to COVID-19, OR
- who require oxygen therapy due to COVID-19, OR
- who require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.

6 OVERALL SAFETY SUMMARY

6.1 Clinical Trials Experience

The safety of bamlanivimab administered with etesevimab is primarily based on exposure of approximately 1400 ambulatory (non-hospitalized) subjects who received doses of bamlanivimab and etesevimab together, at the recommended dose or higher, in BLAZE-1 and BLAZE-4. BLAZE-1 is an ongoing Phase 2/3, randomized, double-blind, placebo-controlled clinical trial studying bamlanivimab and etesevimab administered together for the treatment of subjects with mild to moderate COVID-19. In the Phase 3 portion of the trial, enrolled participants had at least one risk factor for the development of severe COVID-19 illness. BLAZE-4 is an ongoing Phase 2, randomized, double-blind, placebo-controlled clinical trial studying bamlanivimab and etesevimab for the treatment of subjects with mild to moderate COVID-19. Subjects ≥65 years old or with BMI ≥35 were excluded from enrollment. In clinical trials, approximately 4,000 subjects have received bamlanivimab (either alone or with etesevimab) at doses ranging from 700 to 7,000 mg. Bamlanivimab and etesevimab at the authorized doses of 700 mg and 1,400 mg have been administered together to approximately 800 subjects in clinical trials *[see Clinical Pharmacology (14.2)]*.

The following adverse reactions (i.e., adverse events assessed as causally related) have been observed in those who have received bamlanivimab and etesevimab together at the authorized dose or higher *[see Warnings and Precautions (5.1)]*:

- anaphylaxis (n=1, 0.07%)
- infusion-related reactions (n=16, 1.1%)

In the case of anaphylaxis and serious infusion-related reactions, all infusions were stopped, and treatment was administered. One case required epinephrine. All events resolved.

The most common treatment-emergent adverse events in the bamlanivimab and etesevimab treatment group in BLAZE-1 and BLAZE-4 included nausea, dizziness, and pruritus. No treatment-emergent adverse events occurred in more than 1% of participants and the rates were comparable in the treatment and placebo groups.

7 PATIENT MONITORING RECOMMENDATIONS

Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete *[see Warnings and Precautions (5.1) and Overall Safety Summary (6.1)]*.

8 ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS

Clinical trials evaluating the safety of bamlanivimab and etesevimab are ongoing *[see Overall Safety Summary (6)]*.

Completion of FDA MedWatch Form to report all medication errors and serious adverse events* occurring during bamlanivimab and etesevimab use and considered to be potentially related to bamlanivimab and etesevimab is mandatory and must be done by the prescribing healthcare provider and/or the provider's designee. These adverse events must be reported within 7 calendar days from the onset of the event:

*Serious adverse events are defined as:

- death;
- a life-threatening adverse event;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

If a serious and unexpected adverse event occurs and appears to be associated with the use of bamlanivimab and etesevimab under this EUA, the prescribing healthcare provider and/or the provider's designee should complete and submit a MedWatch form to FDA using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
    - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
    - Fax (1-800-FDA- 0178), or
- Call 1-800-FDA-1088 to request a reporting form

IMPORTANT: When reporting adverse events or medication errors to MedWatch, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information to include:

- Patient demographics (e.g., patient initials, date of birth)
- Pertinent medical history
- Pertinent details regarding adverse events and course of illness
- Concomitant medications
- Timing of adverse event(s) in relationship to administration of bamlanivimab and etesevimab
- Pertinent laboratory and virology information
- Outcome of the event and any additional follow-up information if it is available at the time of the MedWatch report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

1. In section A, box 1, provide the patient's initials in the Patient Identifier
2. In section A, box 2, provide the patient's date of birth
3. In section B, box 5, description of the event:
    a. Write "bamlanivimab and etesevimab use for COVID-19 under Emergency Use Authorization (EUA)" as the first line
    b. Provide a detailed report of medication error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved drug. Please see information to include listed above.
4. In section G, box 1, name and address:
    a. Provide the name and contact information of the prescribing healthcare provider or institutional designee who is responsible for the report.
    b. Provide the address of the treating institution (NOT the healthcare provider's office address).

9 OTHER REPORTING REQUIREMENTS

- Healthcare facilities and providers must report therapeutics information and utilization data through HHS Protect, Teletracking or National Healthcare Safety Network (NHSN) as directed by the U.S. Department of Health and Human Services.

- In addition, please provide a copy of all FDA MedWatch forms to:
  Eli Lilly and Company, Global Patient Safety
  Fax: 1-317-277-0853
  E-mail: mailindata_gsmtindy@lilly.com
  Or call Eli Lilly and Company at 1-855-LillyC19 (1-855-545-5921) to report adverse events.

10 DRUG INTERACTIONS

Bamlanivimab and etesevimab are not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Risk Summary

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Bamlanivimab and etesevimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the mother and the fetus.

Nonclinical reproductive toxicity studies have not been performed with bamlanivimab or etesevimab. In tissue cross reactivity studies using human fetal tissues, no binding of

clinical concern was detected for etesevimab or bamlanivimab. Human immunoglobulin G1 (IgG1) antibodies are known to cross the placental barrier; therefore, bamlanivimab and etesevimab have the potential to be transferred from the mother to the developing fetus. It is unknown whether the potential transfer of bamlanivimab or etesevimab provides any treatment benefit or risk to the developing fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

11.2 Lactation

Risk Summary

There are no available data on the presence of bamlanivimab or etesevimab in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bamlanivimab and etesevimab and any potential adverse effects on the breastfed child from bamlanivimab and etesevimab or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

11.3 Pediatric Use

Bamlanivimab and etesevimab are not authorized for use in pediatric patients under 12 years of age or weighing less than 40 kg. The safety and effectiveness of bamlanivimab and etesevimab administered together are being assessed in adolescent patients in ongoing clinical trials. The PK of bamlanivimab 700 mg and etesevimab 1,400 mg has been evaluated in pediatric patients ages 12 years or older who weigh at least 40 kg. The data show that the plasma exposures in these 10 patients are comparable to what has been observed in adult patients at the authorized dose. The PK of bamlanivimab and etesevimab has not been evaluated in pediatric patients ages <12 years who weigh <40 kg.

11.4 Geriatric Use

Of the 1141 patients receiving bamlanivimab and etesevimab in BLAZE-1, 30% were 65 years of age and older and 10% were 75 years of age and older. Based on population PK analyses, there is no difference in PK of bamlanivimab or etesevimab in geriatric patients compared to younger patients *[see Clinical Trial Results and Supporting Data for EUA (18.1)]*.

11.5 Renal Impairment

Bamlanivimab and etesevimab are not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of bamlanivimab or etesevimab.

11.6 Hepatic Impairment

Based on population PK analysis, there is no difference in PK of bamlanivimab or etesevimab in patients with mild hepatic impairment compared to patients with normal

hepatic function. Bamlanivimab and etesevimab have not been studied in patients with moderate or severe hepatic impairment.

11.7 Other Specific Populations

Based on population PK analysis, the PK of bamlanivimab and etesevimab was not affected by sex, race, or disease severity. Body weight had no clinically relevant effect on the PK of bamlanivimab and etesevimab in adults with COVID-19 over the body weight range of 41 kg to 173 kg.

12 OVERDOSAGE

Doses up to 7,000 mg of bamlanivimab (10 times the authorized dose of bamlanivimab) or 7,000 mg of etesevimab (5 times the authorized dose of etesevimab) have been administered in clinical trials without dose-limiting toxicity. Treatment of overdose with bamlanivimab and etesevimab should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with either bamlanivimab or etesevimab.

13 DESCRIPTION

Bamlanivimab
Bamlanivimab is a human immunoglobulin G-1 (IgG1 variant) monoclonal antibody consisting of 2 identical light chain polypeptides composed of 214 amino acids each and 2 identical heavy chain polypeptides composed of 455 amino acids produced by a Chinese Hamster Ovary (CHO) cell line and molecular weight of 146 kDa.

Bamlanivimab injection is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution in a single-dose vial for intravenous infusion after dilution.

Each mL contains 35 mg of bamlanivimab, and L-histidine (0.4 mg), L-histidine hydrochloride monohydrate (0.6 mg), sodium chloride (2.9 mg), sucrose (60 mg), polysorbate 80 (0.5 mg), and Water for Injection. The bamlanivimab solution has a pH range of 5.5-6.5.

Etesevimab
Etesevimab is a human IgG1 variant monoclonal antibody (mAb) consisting of 2 identical light chain polypeptides composed of 216 amino acids each and 2 identical heavy chain polypeptides composed of 449 amino acids produced by a Chinese Hamster Ovary (CHO) cell line and molecular weight of 145 kDa.

Etesevimab injection is a sterile, preservative-free, clear to opalescent and colorless to slightly yellow to slightly brown solution in a single-dose vial for intravenous infusion after dilution.

Each mL contains 35 mg of etesevimab, L-histidine (1.55 mg), L-histidine hydrochloride monohydrate (2.10 mg), sucrose (80.4 mg), polysorbate 80 (0.5 mg), and Water for injection. The etesevimab solution has a pH range of 5.5.-6.5.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

Bamlanivimab is a recombinant neutralizing human IgG1κ monoclonal antibody (mAb) to the spike protein of SARS-CoV-2 and is unmodified in the Fc region. Bamlanivimab binds the spike protein with a dissociation constant K_D = 0.071 nM and blocks spike protein attachment to the human ACE2 receptor with an IC_{50} value of 0.17 nM (0.025 µg/mL).

Etesevimab is a recombinant neutralizing human IgG1κ mAb to the spike protein of SARS-CoV-2, with amino acid substitutions in the Fc region (L234A, L235A) to reduce effector function. Etesevimab binds the spike protein with a dissociation constant K_D = 6.45 nM and blocks spike protein attachment to the human ACE2 receptor with an IC_{50} value of 0.32 nM (0.046 µg/mL).

Bamlanivimab and etesevimab bind to different but overlapping epitopes in the receptor binding domain (RBD) of the S-protein. Using both antibodies together is expected to reduce the risk of viral resistance.

14.2 Pharmacodynamics

A flat exposure-response relationship for efficacy was identified for bamlanivimab and etesevimab administered together within the dose range of 700 mg bamlanivimab and 1,400 mg etesevimab to 2,800 mg bamlanivimab and 2,800 mg etesevimab (4 and 2 times the authorized dose, respectively), based on clinical data and pharmacokinetic/pharmacodynamic modeling.

14.3 Pharmacokinetics

Pharmacokinetic profiles of bamlanivimab and etesevimab are linear and dose-proportional between 700 mg and 7000 mg following a single IV administration. There were no differences in PK of bamlanivimab between severe/moderate participants who were hospitalized and mild/moderate ambulatory participants. There were no differences in PK of etesevimab between mild/moderate ambulatory participants and healthy participants. There is no change in PK of bamlanivimab or etesevimab administered alone or together suggesting there is no interaction between the two antibodies.

Absorption
The mean maximum concentration (Cmax) of 700 mg bamlanivimab was 196 µg/mL (90% CI: 102 to 378 µg/mL) following approximately 1 hour 700 mg IV infusion.

The mean maximum concentration (Cmax) of 1400 mg etesevimab is estimated to be 504 µg/mL (90% CI: 262 to 974 µg/mL) following approximately 1 hour IV infusion.

Distribution
Bamlanivimab mean volume of distribution (V) was 2.87 L and 2.71 L for the central and peripheral compartments, respectively. The between subject variability was 23.2% CV.

Etesevimab mean volume of distribution (V) was 2.38 L and 1.98 L for the central and peripheral compartments, respectively. The between subject variability was 27.8% CV.

Metabolism
Bamlanivimab and etesevimab are expected to be degraded into small peptides and component amino acids via catabolic pathways in the same manner as endogenous IgG antibodies.

Elimination
Bamlanivimab clearance (CL) was 0.27 L/day (between subject variability 22.3% CV) and the mean apparent terminal elimination half-life was 17.6 days (between subject variability 15.8% CV). Following a single 700 mg IV dose, bamlanivimab was quantifiable for at least 29 days. The mean concentration was 22 µg/mL (90% CI: 10.7 to 41.6 µg/mL) on Day 29.

Etesevimab clearance (CL) was 0.128 L/day (between subject variability 33.8% CV) and the mean apparent terminal elimination half-life was 25.1 days (between subject variability 29.2% CV). Following a single 1,400 mg IV dose, etesevimab was quantifiable for at least 29 days. The mean concentration was 111 µg/mL (90% CI: 57.4 to 199 µg/mL) on Day 29.

Special Populations:
The PK profiles of bamlanivimab and etesevimab were not affected by age, sex, race, or disease severity based on a population PK analysis. Body weight had no clinically relevant effect on the PK of bamlanivimab or etesevimab in adults with COVID-19 over the body weight range of 41 kg to 173 kg *[see Use in Specific Populations (11.4, 11.7)]*.

Pediatric population
The PK of bamlanivimab and etesevimab at the authorized dose has been evaluated in 10 pediatric patients ages 12 years or older who weigh at least 40 kg. The data show that the plasma exposures in these patients are comparable to what has been observed in adult patients. The PK of bamlanivimab and etesevimab has not been evaluated in pediatric patients ages <12 years who weigh <40 kg.

Patients with renal impairment
Bamlanivimab and etesevimab are not eliminated intact in the urine. Renal impairment is not expected to impact the PK of bamlanivimab and etesevimab, since mAbs with molecular weight >69 kDa are known not to undergo renal elimination. Similarly, dialysis is not expected to impact the PK of bamlanivimab and etesevimab *[see Use in Specific Populations (11.5)]*.

Patients with hepatic impairment
Based on population PK analysis, there is no significant difference in PK of bamlanivimab or etesevimab in patients with mild hepatic impairment compared to patients with normal hepatic function. Bamlanivimab and etesevimab have not been studied in patients with moderate or severe hepatic impairment *[see Use in Specific Populations (11.6)]*.

Drug interactions:
Bamlanivimab and etesevimab are not renally excreted or metabolized by cytochrome P450 enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

15 MICROBIOLOGY/RESISTANCE INFORMATION

Antiviral Activity

The cell culture neutralization activity of bamlanivimab and of etesevimab against SARS-CoV-2 was measured in a dose-response model quantifying plaque reduction using cultured Vero E6 cells. Bamlanivimab, etesevimab and a 1:1 (weight/weight) ratio of bamlanivimab and etesevimab together neutralized the USA/WA/1/2020 isolate of SARS-CoV-2 with estimated EC_{50} values = 0.14 nM (0.02 µg/mL), 0.97 nM (0.14 µg/mL) and 0.14 nM (0.02 µg/mL), respectively.

Bamlanivimab demonstrated antibody-dependent cell-mediated cytotoxicity on reporter Jurkat cells expressing FcγRIIIa following engagement with target cells expressing spike protein. Bamlanivimab did not elicit complement-dependent cytotoxicity activity in cell-based assays.

Etesevimab did not demonstrate detectable antibody-dependent cell-mediated cytotoxicity on Jurkat reporter cells expressing FcγRIIIa. Etesevimab did not elicit complement-dependent cytotoxicity activity in cell-based assays.

Antibody Dependent Enhancement (ADE) of Infection

The risk that bamlanivimab and etesevimab could mediate viral uptake and replication by immune cells was studied in THP-1 and Raji cell lines and primary human macrophages. In general, experiments with bamlanivimab, with etesevimab, and with bamlanivimab and etesevimab together did not demonstrate productive viral infection in immune cells exposed to SARS-CoV-2 at concentrations of mAb(s) down to at least 100-fold below the respective EC_{50} value(s).

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to bamlanivimab and/or etesevimab (Table 3). Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering treatment options.

Resistant variants were identified using directed evolution of the spike protein and serial passage in cell culture of SARS-CoV-2 in the presence of bamlanivimab or etesevimab individually. Resistant variants were not identified when bamlanivimab and etesevimab were tested together using the same methodology. Viral variants identified in these studies that had reduced susceptibility to bamlanivimab included spike protein amino acid substitutions E484D/K/Q, F490S, Q493R, and S494P, and variants that had reduced susceptibility to etesevimab included substitutions K417N, D420N, and N460K/S/T/Y. Neutralization assays using SARS-CoV-2, pseudotyped vesicular stomatitis virus (VSV) virus-like particles (VLP), or binding assessment if pseudotyped VLP construction was unsuccessful (E484D), confirmed reductions in susceptibility to the selecting antibody. Retention of susceptibility to the other antibody alone was observed, with the exception of the Q493R substitution. All variants maintained susceptibility to bamlanivimab and etesevimab together, with the exception of those with E484K, E484Q, and Q493R substitutions, which had reduced susceptibility of 17-fold, 22-fold, and >100-fold, respectively in a pseudotyped VLP assay.

Evaluation of susceptibility of variants identified through global surveillance in subjects treated with bamlanivimab and etesevimab is ongoing. Pseudotyped VLP evaluation of

amino acid substitutions identified in global surveillance showed that the V483A substitution reduced susceptibility to bamlanivimab 48-fold, but activity was maintained with etesevimab, and with bamlanivimab and etesevimab together. N501Y and N501T substitutions reduced susceptibility to etesevimab approximately 5-fold and 20-fold, respectively. Activity against variants with N501Y or N501T substitutions was maintained with bamlanivimab alone, and with bamlanivimab and etesevimab together.

Bamlanivimab alone and bamlanivimab and etesevimab together retained activity against a SARS-CoV-2 B.1.1.7 lineage (UK origin) virus and related pseudotyped VLPs expressing del69-70 + N501Y found in the B.1.1.7 variant. Pseudotyped VLPs expressing spike protein from the B.1.351 lineage (South Africa origin) or substitutions K417N + E484K + N501Y found in this lineage had reduced susceptibility to bamlanivimab and etesevimab together of 215-fold or >45-fold, respectively, and pseudotyped VLPs expressing spike protein from the P.1 lineage (Brazil origin) or K417T + E484K + N501Y found in the P.1 lineage had reduced susceptibility to bamlanivimab and etesevimab together of >46-fold or >511-fold, respectively. Pseudotyped VLPs expressing spike protein from the B.1.427/B.1.429 lineages (California origin) or the L452R substitution found in this lineage, maintained activity for etesevimab but showed reduced susceptibility to bamlanivimab and etesevimab together of 9-fold or 15-fold, respectively (Table 3).

Table 3: Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions with Bamlanivimab and Etesevimab Together (1:2 Molar Ratio)

Lineage with Spike Protein Substitution	Key Substitutions Tested[a]	Fold Reduction in Susceptibility
B.1.1.7 (UK origin)	N501Y	no change[b]
B.1.351 (South Africa origin)	K417N + E484K + N501Y	215[c]
P.1 (Brazil origin)	K417T + E484K + N501Y	>46[c]
B.1.427/B.1.429 (California origin)	L452R	9[d]
B.1.526 (New York origin)[e]	E484K	31

[a] For variants with more than one substitution of concern, only the substitution(s) with the greatest impact on activity is(are) listed. For B.1.351, P.1 and B.1.427/B.1.429, spike variants reflective of the consensus sequence for the lineage were tested.
[b] No change: <5-fold reduction in susceptibility.
[c] Bamlanivimab and etesevimab together are unlikely to be active against variants from this lineage. No activity observed at the highest concentration tested for the P.1 variant.
[d] Etesevimab retains activity against this variant.
[e] Isolates of the B.1.526 lineage harbor several spike protein amino acid substitutions, and not all isolates contain the E484K substitution (as of February 2021). This assay was conducted using pseudotyped VLPs with the E484K substitution only.

Table 4: Authentic[a] SARS-CoV-2 Neutralization Data for Bamlanivimab and Etesevimab Together (1:2 Molar Ratio)

Lineage with Spike Protein Substitution	Key Substitution Tested[b]	Fold Reduction in Susceptibility
B.1.1.7 (UK origin)	N501Y	no change[c]
B.1.526 (New York origin)[d]	E484K	10.5

[a] The B.1.1.7 variant was assessed using cell culture-expanded virus; the B.1.526/E484K substitution was assessed using recombinant SARS-CoV-2 (USA/WA/1/2020 isolate).
[b] For variants with more than one substitution of concern, only the one(s) with the greatest impact on activity is(are) listed.
[c] No change: <5-fold reduction in susceptibility.
[d] Isolates of the B.1.526 lineage harbor several spike protein amino acid substitutions, and not all isolates contain the E484K substitution (as of February 2021). This assay was conducted using recombinant SARS-CoV-2 with the E484K substitution only.

Due to the lack of pseudotyped VLP neutralization activity of both bamlanivimab and etesevimab against the substitutions in B.1.351 (South Africa origin) and P.1 (Brazil origin), it is unlikely that bamlanivimab and etesevimab together will be active against these variants.

It is unclear how small reductions in susceptibility to bamlanivimab and etesevimab seen in authentic or recombinant SARS-CoV-2 or pseudotyped VLP assays correlate with clinical outcomes. Bamlanivimab alone does not retain activity against variants with E484K. SARS-CoV-2 (USA/WA/1/2020 isolate) engineered to express the E484K substitution present in the B.1.526 lineage (New York origin) retained activity to etesevimab alone but showed reduced susceptibility to bamlanivimab and etesevimab together of 10-fold (Table 4). Available nonclinical and clinical PK data indicate that etesevimab at the authorized dose may retain activity against the B.1.526 variant clinically, although only very limited data are currently available from patients infected with this variant in clinical trials. Preliminary clinical evidence indicates that the administration of bamlanivimab and etesevimab together result in similar viral load reductions in participants infected with the L452R variant (California origin) as observed in those who were infected with bamlanivimab-sensitive strains. Of the 134 participants infected with the L452R variant at baseline in the Phase 3 portion of BLAZE-1, 3 of the 50 individuals treated with placebo (6%) and 1 of the 84 participants treated with bamlanivimab 700 mg and etesevimab 1,400 mg (1%) were hospitalized (p=0.15).

Genotypic and phenotypic testing are ongoing to monitor for potential bamlanivimab- and etesevimab-resistance associated spike variations in clinical trials. Analysis of baseline samples show that 9.8% (163/1662) of clinical trial patients were infected with viral variants containing single amino acid substitutions at positions associated with reduced susceptibility to either bamlanivimab or etesevimab as predicted by pseudotyped VLP neutralization assays. Only 1 patient was infected with a variant (E484G) that was predicted to have reduced susceptibility to both bamlanivimab and etesevimab.

Patient samples were also analyzed for treatment-emergent viral variants, defined as variants with single amino acid substitutions at positions that had reduced susceptibility to either bamlanivimab or etesevimab present at an allele fraction of ≥15%.

- In the Phase 3 portion of BLAZE-1, treatment-emergent variants were observed in 7.1% (30/425) of patients treated with bamlanivimab 2,800 mg and etesevimab 2,800 mg together, in 11.5% (6/52) of patients treated with bamlanivimab 700 mg

and etesevimab 1,400 mg together, and in 3.7% (17/462) of patients treated with placebo.

- In patients treated with bamlanivimab and etesevimab together, substitutions detected in one or more patients included ones with reduced susceptibility (≥5-fold) to bamlanivimab only: L452R, E484K, G485V, and S494P; and ones with reduced susceptibility to etesevimab only: D405G/Y, K417N, D420N, N460T, and N501I/T. While these variants had reduced susceptibility to either bamlanivimab OR etesevimab compared to wild-type in a pseudotyped VSV VLP assay they still retained susceptibility to the other antibody in the combination.
- There were also observations of variants with reduced susceptibility (≥5-fold) to both bamlanivimab and etesevimab: F490L (n=3; 13-fold reduction) and Q493K/R (n=2; >34-fold [Q493K] and >100-fold [Q493R] reductions) out of a total of 579 patients treated with bamlanivimab and etesevimab together.
- Additional treatment-emergent substitutions in patients treated with bamlanivimab and etesevimab together, with no phenotypic data, include D405del, D420Y, N460I, G485D and S494L. The impact of these substitutions is not currently known.

It is possible that bamlanivimab and etesevimab resistance-associated variants could have cross-resistance to other mAbs targeting the receptor binding domain of SARS-CoV-2. The clinical impact is not known.

Immune Response Attenuation

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

16 NONCLINICAL TOXICOLOGY

Carcinogenesis, mutagenesis, and reproductive toxicology studies with bamlanivimab or etesevimab have not been conducted.

In toxicology studies, bamlanivimab and etesevimab had no adverse effects when administered intravenously to rats and monkeys, respectively. Non-adverse increases in neutrophils were observed in rats dosed with bamlanivimab.

In tissue cross reactivity studies using human adult and fetal tissues, no binding of clinical concern was detected for bamlanivimab or etesevimab.

17 ANIMAL PHARMACOLOGIC AND EFFICACY DATA

Antiviral Activity In Vivo

Prophylactic administration of bamlanivimab to female Rhesus macaques (n=3 or 4 per group) resulted in 1 to 4 $\log_{10}$ decreases in viral genomic RNA and viral replication (sub-genomic RNA) in bronchoalveolar lavage samples relative to control animals, but less of an impact on viral RNA in throat and nasal swabs following SARS-CoV-2 inoculation.

Prophylactic or therapeutic administration of etesevimab to male Rhesus macaques (n=3 per group) resulted in approximately 4 or 3 $\log_{10}$ average decreases, respectively, in viral genomic RNA in oropharyngeal swabs at Day 4 post infection relative to control animals.

The applicability of these findings to a prophylaxis or treatment setting is not known.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

The data supporting this EUA are primarily based on analyses of data from the Phase 2/3 BLAZE-1 trial (NCT04427501). This trial provides Phase 3 placebo-controlled clinical efficacy data from subjects receiving 700 mg bamlanivimab and 1,400 mg of etesevimab together, as well as for subjects receiving 2,800 mg bamlanivimab and 2,800 mg etesevimab together.

18.1 Mild to Moderate COVID-19 (BLAZE-1)

BLAZE-1 is an ongoing randomized, double-blind, placebo-controlled clinical trial studying bamlanivimab and etesevimab administered together for the treatment of subjects with mild to moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). BLAZE-1 enrolled adult subjects who were not hospitalized and had at least 1 or more COVID-19 symptoms that were at least mild in severity. Treatment was initiated within 3 days of obtaining the clinical sample for the first positive SARS-CoV-2 viral infection determination. Subjects in the Phase 3 portion of the trial met the criteria for high-risk (as defined in Section 2).

Phase 3 Data from BLAZE-1 (bamlanivimab 700 mg and etesevimab 1,400 mg)
In this portion of the trial, subjects were treated with a single infusion of bamlanivimab 700 mg and etesevimab 1,400 mg (N=511) or placebo (N=258). The majority (99.2%) of the patients enrolled in these dose arms met the criteria for high-risk adults (≥18 years of age) that included at least one of the following: age ≥65 years, BMI ≥35, chronic kidney disease, diabetes, immunosuppressive disease, immunosuppressant treatment, or age ≥55 years with cardiovascular disease, hypertension, chronic pulmonary disease or other chronic respiratory disease. Participants ages 12-17 were also enrolled in the trial (10 [2.0%] were treated with bamlanivimab and etesevimab and 13 [1.7%] were treated with placebo), and met high-risk criteria as defined in the trial protocol.

At baseline, median age was 56 years (with 30% of subjects aged 65 or older); 53% of subjects were female, 87% were White, 27% were Hispanic or Latino, and 8% were Black or African American. Subjects had mild (76%) to moderate (24%) COVID-19; the mean duration of symptoms was 4 days; mean viral load by cycle threshold (CT) was 24.33 at baseline. The baseline demographics and disease characteristics were well balanced across treatment groups.

The primary endpoint was the proportion of subjects with COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause by Day 29. Events occurred in 15 subjects treated with placebo (6%) as compared to 4 events in subjects treated with bamlanivimab 700 mg and etesevimab 1,400 mg together (0.8%) [$p<0.0001$], an 87% reduction. There were 4 deaths in subjects treated with placebo and no deaths in subjects treated with bamlanivimab 700 mg and etesevimab 1,400 mg together ($p=0.01$).

Secondary endpoints include mean change in viral load from baseline to Day 3, 5, and 7 (Figure 1).

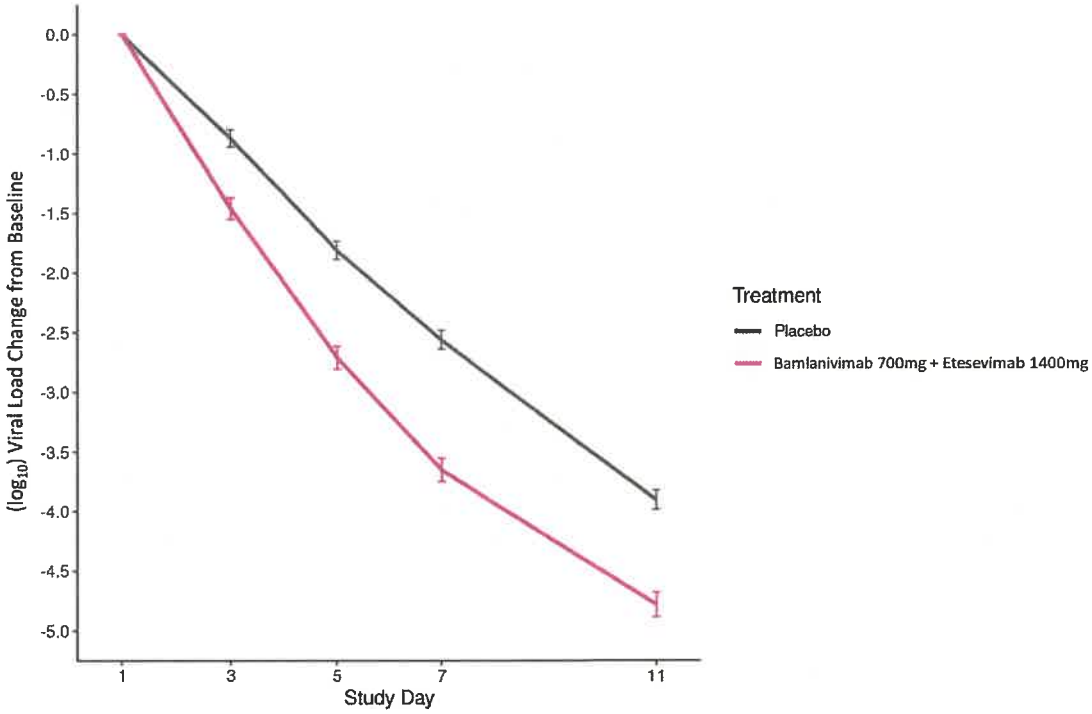

Figure 1: SARS-CoV-2 Viral Load Change from Baseline (Mean ± SE) by Visit from the Phase 3 Portion of BLAZE-1 (700 mg bamlanivimab and 1,400 mg etesevimab).

The median time to sustained symptom resolution as recorded in a trial specific daily symptom diary was 8 days for subjects treated with bamlanivimab 700 mg and etesevimab 1,400 mg together as compared with 10 days for subjects treated with placebo (p=0.009). Symptoms assessed were cough, shortness of breath, feeling feverish, fatigue, body aches and pains, sore throat, chills, and headache. Sustained symptom resolution was defined as absence of any of these symptoms, except for allowance of mild fatigue and cough, in two consecutive assessments.

Phase 3 Data from BLAZE-1 (bamlanivimab 2,800 mg and etesevimab 2,800 mg)
Subjects were treated with a single infusion of bamlanivimab 2,800 mg and etesevimab 2,800 mg (N=518) or placebo (N=517). All of the patients enrolled in these dose arms met the criteria for high-risk adults (≥18 years of age) that included at least one of the following: age ≥65 years of age, BMI ≥35, chronic kidney disease, diabetes, immunosuppressive disease, immunosuppressant treatment, or age ≥55 years with cardiovascular disease, hypertension, chronic pulmonary disease or other chronic respiratory disease. Participants ages 12-17 years were also enrolled in the trial (4 [0.8%] were treated with bamlanivimab and etesevimab and 7 [1.4%] were treated with placebo), and met high-risk criteria as defined in the trial protocol.

Bamlanivimab 2,800 mg and etesevimab 2,800 mg is not an authorized dosage under this EUA. The baseline demographics and disease characteristics were well balanced across treatment groups.

The primary endpoint was the proportion of subjects with COVID-19 related hospitalization (defined as ≥24 hours of acute care) or death by any cause by Day 29. Events occurred in 36 subjects treated with placebo (7%) as compared to 11 events in subjects treated with bamlanivimab 2,800 mg and etesevimab 2,800 mg together (2%) [p<0.001], a 70% reduction. There were 10 deaths in subjects treated with placebo and no deaths in subjects treated with bamlanivimab 2,800 mg and etesevimab 2,800 mg together (p<0.001).

19 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

UNDER THIS EUA, BAMLANIVIMAB AND ETESEVIMAB MUST BE ADMINISTERED TOGETHER.

Bamlanivimab
Bamlanivimab injection is a sterile, preservative-free clear to opalescent and colorless to slightly yellow to slightly brown solution supplied in a single-dose vial.

Etesevimab
Etesevimab injection is a sterile, preservative-free clear to opalescent and colorless to slightly yellow to slightly brown solution supplied in a single-dose vial.

Bamlanivimab and etesevimab are supplied as:

Antibody	Concentration	Package Size	NDC
Bamlanivimab	700 mg/20 mL (35 mg/mL)	one vial per carton	0002-7910-01
Etesevimab	700 mg/20 mL (35 mg/mL)	one vial per carton	0002-7950-01

Storage and Handling

Bamlanivimab is preservative-free. Discard unused portion.
Etesevimab is preservative-free. Discard unused portion.

Store unopened vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.

DO NOT FREEZE, SHAKE, OR EXPOSE TO DIRECT LIGHT.

Solution in vial requires dilution prior to administration. The prepared infusion solution is intended to be used immediately. If immediate administration is not possible, store diluted infusion solution in the refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours and at room temperature (20°C to 25°C [68°F to 77°F]) and for up to 7 hours, including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature prior to administration.

20 PATIENT COUNSELING INFORMATION

Patients treated with bamlanivimab and etesevimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing

personal items, clean and disinfect "high touch" surfaces, and frequent handwashing) according to CDC guidelines. Also see Fact Sheet for Patients, Parents and Caregivers.

21 CONTACT INFORMATION

For additional information visit:
www.BAMandETE.com

If you have questions, please contact:
1-855-LillyC19 (1-855-545-5921)

Literature revised May 14, 2021

Eli Lilly and Company, Indianapolis, IN 46285, USA

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GOBIERNO DE PUERTO RICO
Administración de Seguros de Salud

Carta Normativa 20-1218

18 de diciembre de 2020

A: **ORGANIZACIONES DE MANEJO DE CUIDADO DIRIGIDO (MCOs POR LAS SIGLAS EN INGLES), GRUPOS MEDICOS, MEDICOS PRIMARIOS, FARMACIAS Y PROVEEDORES PARTICIPANTES DEL PLAN DE SALUD DEL GOBIERNO, PLAN VITAL**

RE: **GUIA CLINICA PARA LA ADMINISTRACION DE BAMLANIVIMAB Y REGN-COV2 (Regeneron Pharmaceutical, Inc.)**

Recientemente la administración de Drogas y Alimentos (FDA) por sus siglas en inglés, autorizó, bajo el mecanismo de uso de emergencias (EUA), varios medicamentos o combinaciones de medicamentos para el tratamiento del COVID-19.

Cada uno conlleva criterios y requerimientos únicos que procedemos a resumir, sin intención de ser exhaustivo, por lo que cada proveedor que considere recetar o administrar uno de estos productos debe familiarizarse con las recomendaciones del FDA, las cuales se encuentran en el denominado "factsheet".

BAMLANIVIMAB

La FDA el 9 de noviembre de 2020, emitió una autorización de uso de emergencia de la terapia de anticuerpos monoclonales *Bamlanivimab* para el tratamiento de la enfermedad por coronavirus leve a moderada 2019. Este fármaco está en la etapa de investigación y actualmente no está aprobado para ninguna indicación.

La Administración de Seguros de Salud (ASES), hace referencia a las indicaciones para el uso y administración de *Bamlanivimab* (EUA) disponibles en:
https://www.fda.gov/media/143602/download

- El uso de este medicamento es sólo para tratar COVID-19 leve o moderado en pacientes que tengan 12 años o más y pesen al menos 40 kg, con resultados positivos de la prueba viral directa del SARS-CoV-2 y que tienen **un alto riesgo de progresar a COVID-19 grave** y/u hospitalización.

Como alto riesgo la autorización en el EUA define lo siguiente:

- Alto riesgo de progresión de la enfermedad a severa y/o requerir hospitalización se define como aquellos pacientes que tengan al menos uno (1) de los siguientes criterios:
    - Obesidad, con un índice de masa corporal (BMI) igual o mayor de 35.
    - Padecen de enfermedad renal crónica.
    - Diabetes Mellitus
    - Presentan alguna condición o enfermedad inmunosupresora.
    - Se encuentran en tratamiento con medicamentos inmunosupresores.
    - 65 años o más de edad.
    - Pacientes de 55 años o más y que además presentan enfermedad cardiovascular, incluyendo Hipertensión, y/o enfermedad pulmonar obstructiva crónica u otra condición respiratoria.
- Tienen entre 12 -17 años y alguna de las siguientes condiciones:
    - Un BMI igual o mayor de la percentila 85 para su edad y sexo, según las tablas de crecimiento del CDC.
    - Drepanocitosis (sickle cell disease).
    - Enfermedad cardíaca congénita o adquirida.
    - Trastorno del desarrollo neural.
    - Dependencia de tecnología por condiciones médicas (traqueostomía, gastrostomía o dependiente de ventilación asistida no causada por enfermedad del COVID-19).
    - Asma o condición pulmonar crónica que requiera el uso diario de medicamentos para su control.

El uso de *Bamlanivimab* no está autorizado para las siguientes poblaciones de pacientes:

- Adultos o pacientes pediátricos que están hospitalizados debido a COVID-19, o
- Adultos o pacientes pediátricos que requieren oxigenoterapia debido a COVID-19, o
- Adultos o pacientes pediátricos que requieren un aumento en la tasa de flujo de oxígeno inicial debido a COVID-19 en aquellos pacientes en oxigenoterapia crónica debido a un subyacente no relacionado con COVID-19 comorbilidad.
- Pacientes que están hospitalizados con el COVID-19, o
- Adultos o pacientes pediátricos que requieren un aumento en la tasa de flujo de oxígeno inicial debido a COVID-19 en aquellos pacientes en oxigenoterapia crónica debido a un subyacente no relacionado con COVID-19 comorbilidad.

El Bamlanivimab sólo puede administrarse en entornos donde los proveedores de atención médica tengan acceso inmediato a medicamentos para tratar una reacción grave a la infusión, como anafilaxia y la capacidad de activar el sistema médico de emergencia (EMS), según sea necesario.

La autorización para distribución de este medicamento, a facilidades de salud y/o proveedores, estará según la dirección del Gobierno de los Estados Unidos en colaboración con las autoridades gubernamentales estatales. A su vez, este medicamento será provisto por el Gobierno Federal. No obstante, **los costos de administración son parte de la cubierta de beneficios del Plan Vital**. Por tanto, los proveedores de salud deben facturar a los MCOs los servicios asociados a la administración de este medicamento.

CODIFICACION ESTANDAR PARA LA FACTURACION DE SERVICIOS

El Centro de Medicare y Medicaid (CMS, con sus siglas en inglés) estableció la siguiente codificación para los productos o medicamentos de anticuerpos monoclonales y su administración:

Code	*CPT Short Descriptor*	*Labeler Name*	*Vaccine/Procedure Name*
Q0239	Bamlanivimab-xxxx	Eli Lilly	Injection, Bamlanivimab 700 mg
M0239	Bamlanivimab-xxxx Infusion	Eli Lilly	Intrevenous infusion, Balmlanivimab-xxxx, includes infusion and post administration monitoring
Q0243	Casirivimab and Imdevimab	Regeneron	Injection, Casirivimab and Imdevimab, 2400 mg.
M0243	Casirivi and Indevi Infusion	Regeneron	Intravenous infusion, Casirivimab and Imdevimab includes infusion

Incluimos como referencia los siguientes documentos sobre el Bamlanivimab:

Bamlanivimab Factsheet
Formulario para Solicitar Bamlanivimab
Carta Secretario de Salud

REGN-COV2 (Regeneron Pharmaceutical Inc. ROCHE)

El 21 de noviembre de 2020 el FDA emitió una autorización de uso de emergencia (EUA) para el Casirivimab y el Imdevimab, para ser administrados, ambos juntos en combinación, para pacientes adultos y pediátricos de 12 años o más, con un peso de 88 libras o más (40 kg.), que tengan una prueba viral para COVID-19 positiva con manifestaciones de la enfermedad leve a moderada y que sean pacientes de alto riesgo de progresar a una forma severa de la enfermedad que requiera hospitalización.

Es un medicamento de la categoría denominada anticuerpos monoclonales recombinantes al igual que el Bamlanivimab. La administración es por vía intravenosa en **una sola** infusión de 1200 mg./1200 mg.

LIMITACIONES DE USO

No está autorizado su uso en pacientes:

- Que se encuentren hospitalizados o
- Que requieran oxígeno suplementario o
- Que requieran uso de oxígeno basal suplementario por condiciones comórbidas y no relacionadas al COVID-19.

El EUA define los pacientes de alto riesgo son:

- Alto riesgo de progresión de la enfermedad a severa y/o requerir hospitalización se define como aquellos pacientes que tengan al menos uno (1) de los siguientes criterios.
- Obesidad, con un índice de masa corporal (BMI) igual o mayor de 35.
- Padecen de enfermedad renal crónica.
- Diabetes Mellitus
- Presentan alguna condición o enfermedad inmunosupresora.
- Se encuentran en tratamiento con medicamentos inmunosupresores.
- 65 años o más de edad.
- Pacientes de 55 años o más y que además presentan enfermedad
- cardiovascular, incluyendo Hipertensión, y/o enfermedad pulmonar obstructiva crónica u otra condición respiratoria.
- Tienen entre 12 -17 años y alguna de las siguientes condiciones:

- Un BMI igual o mayor de la percentila 85 para su edad y sexo, según las tablas de crecimiento del CDC.
- Drepanocitosis (sickle cell disease).
- Enfermedad cardíaca congénita o adquirida.
- Trastorno del desarrollo neural.
- Dependencia de tecnología por condiciones médicas (traqueostomía, gastrostomía o dependiente de ventilación asistida no causada por enfermedad del COVID-19.
- Asma o condición pulmonar crónica que requiera el uso diario de medicamentos para su control.

La ASES reconoce la importancia que los proveedores de salud tengan esta valiosa información y el fiel cumplimiento de los MCOs con estas directrices, que proveen el acceso al tratamiento adecuado a nuestros beneficiarios ya sea que estén hospitalizados o evitando su progresión a estadios graves.

Cordialmente,

Yolanda García Lugo, MS, MBA
Sub Directora ASES

Anejos (3)